DOI:
10.1016/j.ajog.2018.04.009

Document Version
Peer reviewed version

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PII: S0002-9378(18)30287-4

DOI: 10.1016/j.ajog.2018.04.009

Reference: YMOB 12133

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 23 March 2018

Accepted Date: 2 April 2018

Please cite this article as: Romero R, Conde-Agudelo A, Nicolaides KH, There is insufficient evidence to claim that cerclage is the treatment of choice for patients with a cervical length <10mm, *American Journal of Obstetrics and Gynecology* (2018), doi: 10.1016/j.ajog.2018.04.009.

There is insufficient evidence to claim that cerclage is the treatment of choice for patients with a cervical length <10mm

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We thank Dr Powel et al for their interest in our report as well as in the optimal treatment of patients with a short cervix. The Letter to the Editor raised some questions about the prevention of preterm birth in women with a singleton gestation and an extremely short cervix, defined as a cervical length <10 mm.

First, we would like to reaffirm that our individual patient data (IPD) meta-analysis clearly showed that vaginal progesterone significantly reduced the risk of preterm birth <33 weeks of gestation in women with a singleton gestation and a cervical length ≤25 mm, regardless of their history of previous spontaneous preterm birth (relative risk [RR], 0.65; 95% confidence interval [CI], 0.45-0.94 for women with no previous spontaneous preterm birth, and RR, 0.59; 95% CI, 0.40-0.88 for women with previous spontaneous preterm birth).[1] The quality of the evidence in support of this conclusion was graded as high, which means that the true effect lies close to that of the estimate of the effect, and that further research is very unlikely to change this estimate.[2]

Second, a subgroup analysis according to cervical length showed that vaginal progesterone did not appear to decrease the risk of preterm birth <33 weeks of gestation in women with a cervical length <10 mm (RR, 0.97; 95% CI, 0.59-1.59). Given that the confidence interval overlaps with those of women with a cervical length between 10-20 mm (0.42-0.81) and 21-25 mm (0.22-1.38) and that the interaction *P* value for subgroup differences was non-significant (0.22), it is likely that the beneficial effect of vaginal progesterone on the risk of preterm birth <33 weeks of gestation does not differ significantly between patients with a cervical length <10 mm and those with a cervical length between 10-25 mm. This is the standard interpretation of an interaction *P* value for subgroup differences, which addresses the likelihood

that chance explains the apparent differences in effect across subgroups and helps to avoid spuriously positive or negative subgroup findings.[3]

It is important to note that the beneficial effect of vaginal progesterone on the risk of composite neonatal morbidity and mortality did not differ significantly between women with a cervical length <10 mm (RR, 0.68; 95% CI, 0.33-1.41) and those with a cervical length between 10-25 mm (RR, 0.59; 95% CI, 0.35-0.99) (*P* value for interaction=0.75).

Third, the IPD meta-analysis published by Berghella et al[4] reported that the rates of preterm birth <37, <35, <34, <32, <28, and <24 weeks of gestation and adverse perinatal outcomes were not significantly different between the cerclage and no cerclage groups in women without a history of previous spontaneous preterm birth and a cervical length <25 mm. However, the quality of evidence was graded as low, which means that the true effect may be substantially different from the estimate of the effect of the study, and that further research is very likely to change this estimate.[2] A subgroup analysis found that, among women with a cervical length <10 mm, cerclage was associated with a significant decrease in the risk of preterm birth <35 weeks of gestation (RR, 0.68; 95% CI, 0.47-0.98). The authors correctly concluded that "cerclage seems to be possibly efficacious" in this subgroup of women and recommended that "well-powered trials should be carried in these patients."

Fourth, subgroup analyses are known to have limitations such as false-positive results due to multiple comparisons, false-negative results due to inadequate power, and a limited ability to inform individual treatment decisions because patients have multiple characteristics that vary simultaneously.[3] Even when performed correctly, most differences in treatment efficacy derived from subgroup analyses prove to be spurious and, therefore, should be considered hypothesis-generating rather than hypothesis-testing.[3]

The findings described in the subgroup analyses of the IPD meta-analyses by Berghella et al[4] and our team[1] regarding the efficacy of cerclage and vaginal progesterone in women with a cervical length <10 mm are exploratory and hypothesis-generating analyses, which require confirmatory research. These exploratory analyses should be considered tentative, until confirmed or refuted by subsequent studies.

In conclusion, we recommend that clinicians:

- continue to perform universal transvaginal cervical length screening at 18–24 weeks of gestation in women with a singleton gestation and to offer vaginal progesterone to those with a cervical length ≤25 mm, regardless of the history of previous spontaneous preterm birth, with the aim of preventing preterm birth and reducing neonatal morbidity and mortality.[5] This strategy has proven to be cost-effective and to reduce preterm birth rates when universally implemented;
- consider that cerclage has been shown to reduce the risk of preterm birth and adverse perinatal outcomes in women with a singleton gestation, history of previous spontaneous preterm birth, and a cervical length <25 mm; thus, it can also be offered to patients with these characteristics.[5] Other factors, such as adverse events and cost-effectiveness of interventions, and patient/physician preference, should be taken into consideration when counseling patients;
- be aware that there is insufficient evidence to support the use of cerclage in patients with a short cervix in the absence of a history of preterm birth.

We believe that further randomized controlled trials to assess the efficacy and safety of vaginal progesterone vs cerclage in women with a cervical length <10 mm are warranted.

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The authors report no conflict of interest

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